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Ketamine sedation in mechanically ventilated patients: A systematic review and meta-analysis

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TITLE PAGE

Title: Ketamine sedation in mechanically ventilated patients: a systematic review and meta-analysis

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ABSTRACT

Purpose: Ketamine use as a sedative agent in mechanically ventilated patients is increasing. This systematic review and meta-analysis collates existing literature and quantifies the impact of ketamine in mechanically ventilated patients.

Materials and Methods: EMBASE, MEDLINE, Scopus, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, conference proceedings, and reference lists were searched. Randomized and nonrandomized studies were included, and two reviewers independently screened abstracts of identified studies for eligibility.

Results: Fifteen studies (n= 892 patients) were included. Random effects meta-analytic models revealed that ketamine was associated with a reduction in propofol infusion rate (mean difference in dose, -699 mcg/min; 95% CI -1169 to -230, p =0.003), but had no impact on fentanyl or midazolam. Ketamine was not associated with mortality, on-target sedation, vasopressor dependence, or hospital length of stay. Cardiovascular complications (e.g. tachycardia and hypertension) were most commonly reported, followed by neurocognitive events, such as agitation and delirium.

Conclusions: The data regarding ketamine use in mechanically ventilated patients is limited in terms of quantity, methodological quality, and demonstrated clinical benefit. Ketamine may play a role as a sedative-sparing agent, but may be associated with harm. High-quality studies are needed before widespread adoption of ketamine earlier in the sedation pathway.

KEYWORDS

Ketamine, sedation, mechanical ventilation

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ABBREVIATIONS LIST

CENTRAL: Cochrane Central Register of Controlled Trials
ICU: Intensive care unit
ICP: Intracranial pressure
MOOSE: Meta-analysis of Observational Studies in Epidemiology
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis
RASS: Richmond Agitation-Sedation Scale
RCT: randomized controlled trial
RevMan: Review Manager

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INTRODUCTION

Mechanically ventilated patients experience high mortality, survivor morbidity, and account for significant cost within the healthcare system [1]. The provision of analgesia and sedation is a near-ubiquitous intervention, and the approach to analgosedation influences outcome in mechanically ventilated patients [2]. Given the impact of sedation on patient-oriented outcomes, optimizing sedation strategies is a clinical and research priority in critical care.

Ketamine can achieve diverse effects, serving as an anesthetic, sedative, and dissociative agent via N-methyl-D-aspartate receptor antagonism, along with μ and κ opioid receptor agonism. It has also been shown to have anti-inflammatory and neuroprotective properties, along with bronchodilatory effects and a favorable hemodynamic profile, providing potential mechanistic and clinical benefit in critically ill patients with respiratory failure [3-5]. Data suggest that ketamine can decrease the quantity of opioids and benzodiazepines administered, and the incidence and severity of their side effects [6]. A systematic review that included only one randomized controlled trial (RCT) related to the primary outcome (i.e. morphine consumption) concluded that ketamine may decrease analgesic consumption in the intensive care unit (ICU) [7]. However, this prior systematic review conducted only a limited electronic search and did not specifically focus on mechanically ventilated patients. Furthermore, other studies have been published since this review and current critical care guidelines only provide a conditional recommendation (very low quality of evidence) regarding the use of low-dose ketamine as an adjunct to opioids [2]. Ketamine can also have adverse effects, such as an increased incidence of worrisome neuropsychiatric complications, including hallucinations and nightmares [8].

Given these facts, quantifying the existing literature regarding its use in mechanically ventilated patients is warranted before recommending widespread use, and to provide informative data regarding: 1) practice patterns; 2) clinical outcomes; and 3) future clinical investigation. Therefore, the objectives of this study were to perform a comprehensive systematic review of the global literature, including

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RCTs and observational studies, to evaluate ketamine use in mechanically ventilated patients. Based on a scoping review, we hypothesized that ketamine would be associated with a reduction in analgesics and sedatives, but would not be associated with any patient-oriented outcome.

METHODS AND ANALYSIS

Protocol and Registration

This systematic review was designed, conducted, and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [9, 10] (Supplementary Tables S1 and S2). The systematic review was registered in the PROSPERO international prospective registry (#CRD42018095785). Ethical approval was not required.

Study Identification

A written protocol that was finalized prior to beginning was followed (Supplementary Text 1). All search strategies and written methodology were created using the standards and guidelines for conducting and reporting systematic reviews set forth by PRISMA, the National Academies Standards for Systematic Reviews, the Cochrane Handbook of Systematic reviews, and the Peer Review of Systematic Search Strategies. The published literature was searched, in consultation with a medical librarian (LHY), using strategies for the concepts of critical care, artificial respiration, ketamine, fentanyl, morphine, hydromorphone, dexmedetomidine, propofol and benzodiazepines.

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The search strategies were established using a combination of standardized terms and key words and implemented in Embase, Ovid Medline, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov. All searches were completed in July, 2019. Fully reportable searches are in Supplementary Text 1.

Reference lists of included studies were manually screened to identify additional studies. Manual search of abstracts from the following meetings (2010-2019) identified unpublished data: Society of Critical Care Medicine, European Society of Intensive Care Medicine, American Thoracic Society, International Symposium on Intensive Care and Emergency Medicine, Pharmacotherapy, and the Society for Academic Emergency Medicine. The principal investigators were contacted via electronic mail for clarification of data as needed.

Inclusion Criteria

Studies were eligible regardless of language and included adult mechanically ventilated patients receiving continuous intravenous ketamine infusion for sedation. Randomized trials and nonrandomized studies (prospective and retrospective cohort studies, cross-sectional studies, before-after trials, and case studies/series) were all included. Inclusion of nonrandomized studies was decided *a priori* for the following reasons: 1) high likelihood the question of interest could not be investigated with RCTs alone secondary to lack of existing randomized trials; 2) to provide an explicit evaluation of strengths and weaknesses of the current literature; 3) to assess evidence of effects (benefit and harm); and 4) to provide evidence for undertaking randomized trials [11]. Studies that did not report pre-intervention and post-intervention data, such as effects of ketamine on analgosedation requirements, were excluded. Reviews, correspondences, and nonhuman studies were excluded. Eligible studies had to report some outcome of interest to be included.

We compared outcomes between patients receiving ketamine infusions to those receiving other sedatives. The primary outcome was the difference in analgosedation medication dosages (i.e. fentanyl, midazolam, propofol) associated with ketamine use. Secondary

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outcomes included mortality, duration of ventilation, hospital and ICU lengths of stay, delirium incidence, on-target/goal sedation levels, and vasopressor use. A qualitative report regarding ketamine dosing, and adverse events associated with ketamine was also an aim of interest.

Study Selection and Data Abstraction

Two independent reviewers (ATM and RJS) initially screened abstracts of identified studies for eligibility. In cases of disagreement, a third reviewer (BMF) arbitrated consensus. All studies deemed potentially relevant after the screen were obtained and full manuscripts were reviewed.

Data were abstracted using standardized forms. Study characteristics, including author, publication year, number of patients, study design, study quality, risk of bias, ketamine dosing, and outcomes, were collected.

Assessment of Bias and Study Quality

Clinical trials were evaluated for risk of bias with the Cochrane Risk of Bias Tool for RCTs [12]. Domains within each study were deemed to have high, low, or unclear risk of bias based on the this tool, which examines risk of bias including selection, blinding, performance, detection, attrition, and reporting. The overall risk of bias within each trial was determined according to the suggested framework provided by Higgins et al.: 1) low risk- low risk of bias for all key domains; 2) unclear risk- low or unclear risk of bias for all key domains; and 3) high risk- high risk of bias for one or more key domains [13]. Observational studies were assessed for quality with the Newcastle Ottawa Scale, which has a maximum score of nine points [14]. Five or fewer points indicated poor quality.

Data Analysis

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A meta-analytic approach was used to analyze the data, using Review Manager (RevMan, Version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Random effects models (inverse variance) were used to calculate pooled effect sizes and corresponding 95% CIs between ketamine and no ketamine groups. Odds ratios were calculated for binary outcomes. Continuous variables were reported as mean differences (measures of absolute change). To allow for comparison, changes in analgosedation medication doses were standardized according to the most commonly reported dose across studies (e.g. fentanyl- mcg/hr; midazolam- mg/hr; propofol- mcg/min). These medication doses were compared pre- and post-ketamine for observational studies, and ketamine versus no ketamine for the RCTs. Overall effect estimates were generated using a Z test, and *P*-value of < 0.05 was considered statistically significant. Heterogeneity between studies was assessed using I^2 statistic. Publication bias was assessed using a funnel plot of the size of treatment effect against precision of the study. Ketamine dosing and adverse events were reported qualitatively.

After completion of the systematic review, principal investigators were contacted as needed in order to acquire or clarify data that might have been appropriate for meta-analysis. In situations where a lack of analyzable outcome data was present, a *post hoc* decision was made to also qualitatively report study findings along with the results of the meta-analysis in order to report findings as transparently as possible.

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RESULTS

Search and Selection

The comprehensive digital search yielded 1454 potentially relevant publications, of which 26 duplicate studies were removed. Twenty-six were selected for full-text review, and in the final analysis, 15 studies were included [15-28]. Figure 1 displays the details of study selection and exclusion.

Study Characteristics

Fourteen of the studies were published in 2014 or after. There were 3 randomized studies and 12 observational (10 retrospective cohort studies). Four studies were published as conference abstracts, and eleven as peer-reviewed manuscripts. The total number of patients was 892.

The characteristics of included studies are in Table 1. In the randomized studies, the overall risk of bias was unclear in two studies and low in one study, according to the Cochrane collaboration tool. Six nonrandomized studies rated as high quality and six poor quality. Bias assessment and study quality details can be found in Supplementary Table S3. Six of the studies' primary outcomes were related to changes in analgesic and sedative medications associated with ketamine use. Sedation scores and on-target sedation were reported as an outcome in eight studies.

In the three RCTs, ketamine dosing was highly variable, including: 1) a static dose of 0.20 mg/kg/hour [29]; 2) titration between 0.2-0.7 mg/hg/hour to achieve target sedation [16]; and 3) a mean dose of 4.92 mg/kg/hour [15]. Ketamine dosing in the nonrandomized studies was also highly variable, and not reported in three studies. Data regarding starting doses, mean and median infusion rates, ranges, and duration of therapy are provided in Table 1.

Adverse events were variably reported overall, and mentioned in 8 studies (Supplementary Table S4). Cardiovascular complications (e.g. tachycardia and hypertension) were most commonly reported, followed by neurocognitive events, such as agitation and delirium.

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Intracranial pressure (ICP) was reported as a secondary outcome in 2 studies. Neither study found ketamine use to be associated with an increase in ICP [15, 22].

Meta-Analysis

For the primary outcome, changes in analgesic and sedative medications pre- and post-ketamine were compared (Figure 2). Ketamine was not associated with a reduction in fentanyl dose (n= 6 studies, 320 patients; mean difference, -21.5 mcg/hour [95% CI -48.2 – 5.1] *p*= 0.11). In one RCT, there was also no difference in daily consumption of remifentanil between the ketamine and placebo group (162 patients; mean difference -1.4 mcg/kg/hr), *p*= 0.55 [29]. Ketamine was not associated with a reduction in midazolam dose (n= 5 studies, 249 patients; mean difference -0.3 mg/hour [95% CI -0.95 – 0.35], *p*= 0.37). Ketamine was associated with a significant reduction in propofol dose (n= 6 studies, 352 patients; mean difference, -699 mcg/min [95% CI -1,168 to -230], *p*= 0.003). Funnel plot analyses for each of these outcomes are presented in Supplementary Figure 1 and revealed possible reporting bias.

Results for the remainder of the continuous clinical outcomes are in Figure 3. Analyzable data was reported in four studies (n= 312) for ICU length of stay. Ketamine sedation was associated with significantly longer ICU length of stay (mean difference, 2.4 days [95% CI, 1.3 – 3.5], *p* <0.001). One study qualitatively reported “no difference” in ICU length of stay, and another reported that patients receiving ketamine had significantly increased lengths of stay [23, 27]. For hospital length of stay, analyzable data was reported in three studies (n= 173). There was no difference in hospital length of stay (mean difference, 0.5 days [95% CI -6.0 – 7.0], *p*= 0.88). Three studies (n= 287) presented data on mechanical ventilation duration, showing no difference between groups (mean difference, 0.4 days [-0.6 – 1.4], *p*= 0.47) [21, 28, 29].

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Forest plots for binary outcomes are presented in Figure 4. Mortality in patients receiving ketamine was 30.5% compared to 30.8% with no ketamine (n= 6 studies, odds ratio 1.13 (95% CI 0.70 to 1.81), *p*= 0.61 [15, 19, 21, 22, 28, 29]. One study qualitatively reported no difference in mortality associated with ketamine [18]. Eight studies reported the impact of ketamine on sedation levels or achievement of goal sedation; five studies had analyzable data reported as either number of measurements at goal sedation or number of patients at goal sedation. Ketamine was not associated with ability to achieve goal sedation, odds ratio 0.51 (95% CI 0.14 to 1.88), *p*= 0.31. Qualitative reporting on sedation levels (no analyzable data) demonstrated the following with respect to ketamine: 1) "higher" sedation scores associated with ketamine [16]; 2) no difference in proportion of time at RASS goal [20]; and 3) greater time within target RASS [23]. Ketamine was not associated with a decrease in vasopressor dependence (n= 3 studies), odds ratio 1.29 (95% CI 0.83 – 1.98), *p*= 0.25. Qualitative reporting on vasopressor use demonstrated: 1) a trend toward greater vasopressor use in the no-ketamine group [15]; 2) 56.3% of patients with reduced vasopressors associated with ketamine [22]; and 3) a trend toward a lower norepinephrine requirement in the ketamine group [28]. The impact of ketamine on delirium was reported in four studies. The incidence of delirium associated with ketamine was 38.7% compared to 52.5% with no ketamine (n= 2 studies, odds ratio 0.48 (95% CI 0.26 to 0.87), *p*= 0.02 in the two studies that provided data [21, 29]. The remaining two studies qualitatively reported that ketamine was associated with: 1) no difference in delirium incidence [18]; and 2) an increased incidence of ICU delirium [23].

Statistical heterogeneity as described by the I^2 test was 0% for the outcomes of ICU length of stay, mechanical ventilation duration, mortality, and delirium. It was high across the remainder of the clinical outcomes, and is displayed with the forest plots of each outcome.

DISCUSSION

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Mechanically ventilated patients are primarily sedated with some combination of fentanyl, propofol, and midazolam, with increasing use of dexmedetomidine [30-32]. Given the hemodynamic derangements associated with propofol and dexmedetomidine, and negative outcome data associated with benzodiazepines, ketamine has seen increased use in recent years [33]. With the rise of opioid abuse, ketamine could also play a role in treatment of opioid-tolerant patients, mitigation of chronic intensive care-related pain, and iatrogenic opioid withdrawal syndrome in the ICU [34]. However, a lack of comprehensive knowledge regarding adverse effects of continuous ketamine infusions, and the risk of neuropsychiatric symptoms associated with ketamine, raise safety concerns as well [8]. This systematic review and meta-analysis was therefore undertaken to assess outcomes associated with ketamine sedation in mechanically ventilated patients.

Our first finding is the increasing frequency with which ketamine seems to be used in mechanically ventilated patients, as demonstrated by the fact that every study (97.2% of included patients) was published since 2014, except one. This is especially interesting when considering the analysis also demonstrated: 1) a lack of evidence overall; 2) low quality of evidence that does exist; and 3) a lack of patient-oriented outcome data. There was also significant heterogeneity demonstrated statistically between studies and clinically between patients, and in the descriptive data related to ketamine dosing. This suggests that the optimal clinical situation, patient cohort, and approach to dosing are unknown at this time.

With respect to the primary outcome, ketamine has been shown to reduce opioid requirements for surgery patients in the peri-operative period [35, 36]; this finding was not reproduced in a large pragmatic trial [8]. Similarly, and contrary to our hypothesis, we did not observe an opioid-sparing effect of ketamine. With respect to sedation, ketamine may have a role as a sedation-sparing agent, as demonstrated by a significant reduction in propofol dose. However we did not see any decrease in midazolam associated with ketamine. These studies measured changes in a before-after fashion, and therefore should be interpreted with caution. It is possible that changes in

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concomitant sedatives reflect other processes of care (e.g. spontaneous awakening and breathing trials) and ketamine confers no benefit as an analgesic- or sedative-sparing drug.

Regarding clinical outcomes, the majority of studies did not assess patient-oriented outcomes as a primary objective, favoring surrogate outcomes, such as sedation scores and changes in analgesics and sedatives. Based on the quality and quantity of data uncovered in this systematic review, any recommendations regarding ketamine use as a means to improve patient-centered outcomes is very weak. Our observed increased ICU length of stay potentially suggests the opposite, yet there was a reduction in the incidence of delirium; these conflicting results further highlight the heterogeneity and unknowns regarding ketamine sedation for mechanically ventilated patients. Further, adverse events associated with ketamine appear to be fairly common, especially considering a lack of reporting of some key patient-centered complications, such as hallucinations and nightmares. Robust clinical outcome data and comprehensive assessments of adverse events associated with ketamine use in mechanically ventilated patients are lacking, leaving a significant knowledge gap on the risk vs. benefit of its use.

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LIMITATIONS

This systematic review has several limitations. Due to lack of data regarding ketamine use in mechanically ventilated patients, observational studies, randomized trials, and unpublished data were included. This increases risk of bias, yet we have adhered to all reporting guidelines for assessing bias, quality, and transparent reporting of results. Confounding was very likely present within the observational studies. It is possible that more severely ill patients or those that were difficult to sedate (i.e. confounding by indication) received ketamine. Further, as ketamine was used in conjunction with other analgesics and sedatives, we are unable to determine the

efficacy of ketamine as an initial sedative. These issues cannot be resolved with these data. Statistical and clinical heterogeneity were high. As an example, there was no standardization with respect to timeframe among patients receiving ketamine in a before versus after fashion. While limiting the ability to draw any strong conclusions based on these results, it is an important finding as it demonstrates that large-scale studies that are rigorous and transparently reported are needed. There was a lack of transparency in reporting in some studies, requiring us to use both qualitative and quantitative reporting methods. Given what appears to be a steep increase in ketamine publications since 2014, it is possible that we did not find all relevant publications. Our search was aided by a medical librarian and was exhaustive, giving confidence that the largest amount of data on this topic to date has been uncovered.

CONCLUSIONS

The data regarding ketamine use in mechanically ventilated patients is limited both in terms of quantity, methodological quality, and demonstrated clinical benefit. Ketamine may play a role as a sedative-sparing agent, but may be associated with harm. High-quality studies are needed before widespread use or adoption of ketamine earlier in the sedation pathway.

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Author contributions: BMF conceived and designed the study, supervised conduct of the study, screened studies for inclusion in the analysis, managed data, analyzed and interpreted data. ATM designed the study, screened studies for inclusion in the analysis, managed and interpreted data. RJS screened studies for inclusion in the analysis, analyzed and interpreted data. LHY assisted with design of the study, designed and performed the electronic search, analyzed and interpreted data. BWR assisted with design of the study, analyzed and interpreted data, and provided methodological oversight. All authors contributed to the drafting of the manuscript, revision of the manuscript, and approval of the final version.

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Table 1. Included Study Characteristics

Author, Yr, Country	N	Primary Outcome Assessed	Secondary Outcomes Assessed	Overall bias Assessment[a]	Randomization Allocations	Ketamine Dosing	Comments
Randomized Studies							
Bourgoin et al, 2003, France	25	Glasgow Outcome Scale (GOS) at 6 months*	ICP, CPP, daily ICP elevations, mortality, ICU LOS, adverse events, cost*	Unclear risk of bias	Continuous infusion of ketamine-midazolam vs. sufentanil-midazolam	Mean 4.9mg/kg/hr (± 1.5) (Originally reported in mcg/kg/min)	Only 12 patients (of 25) received ketamine. Patient cohort- severe TBI
Gupta et al, 2016, Not stated	60	Pain and sedation scores*	Adverse events*	Unclear risk of bias	Ketamine + dexmedetomidine vs. dexmedetomidine	Started 0.5mg/kg/hr Titrated 0.2-0.7 mg/kg/hr to achieve target sedation	Abstract only, post-op patients after oncological procedures
Perbet et al, 2018, France	162	Total daily consumption of opiates	Presence and duration of delirium, dose of opiates required for equi-analgesia, mortality, delirium- and coma-free days, ICU-free days, ventilator-free days	Low risk of bias	Continuous infusion of ketamine vs. normal saline placebo infused at same rate	0.20mg/kg/hr	The reporting of Table 1 characteristics and other treatment variables was overall sparse
Author, Yr, Country	**N**	**Primary Outcome Assessed**	**Secondary Outcomes Assessed**	**Quality Assessment[b]**	**Study Design**	**Ketamine Dosing**	**Comments**
Nonrandomized Studies							

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Winings et al, 2014, United States	48	Time from maximum fentanyl rate until discontinuation	Duration of mechanical ventilation, length of stay	Good quality, low risk of bias	Retrospective cohort	Not reported	Abstract only, trauma patients
Umunna et al, 2015, United States	30	Adverse events (tachyarrhythmias, hypersalivation, agitation, etc)	Average motor activity assessment score (MAAS), concurrent opiate use	Poor quality, high risk of bias	Retrospective cohort	Starting dose 0.5 mg/kg/hr Mean 2.0 mg/kg/hr (± 0.98) Range 0.5 mg/kg/hr Duration 59.6 hours	Demographics of the cohort unclear
Von der Brelie, 2016, Germany	65	Development of delayed cerebral ischemia – associated cerebral infarctions and Glasgow Outcome Scale at discharge and 3 months*	ICU and hospital LOS, mortality, ICP elevation, vasopressor use	Good quality, low risk of bias	Retrospective cohort	Titrated to a maximum dose of 500mg/hr	Only 41 patients received ketamine. Patient cohort was aneurysmal SAH.
Quisilema-Cadena et al, 2017, Cuba	18	Successful extubation time (from time of intubation to 48 hours after)	Sedation level (RASS), Adverse events, LOS (ICU and hospital), ICU and in-hospital mortality	Good quality, low risk of bias	Prospective cohort	Bolus of 0.3mg/kg Range 0.05-0.4 mg/kg/hr Mean .003mg/kg/hr (± .008)	Morphine-Midazolam (control) compared to Ketamine-Midazolam
Garber et al, 2017, United States	104	Relative change in sedative and analgesia dose 24 hours after ketamine initiation	On target sedation, adverse events, delirium	Good quality, low risk of bias	Retrospective cohort, before-after	Mean 0.42 mg/kg/hr (± 0.03) Median duration of 90.5 hours (55.9–148.0)	Demographics of the cohort (i.e. surgical vs. medical) unclear

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Shurtleff et al, 2017, United States	79	Days alive without delirium or coma	Delirium at any point during ICU stay, duration of mechanical ventilation	Good quality, low risk of bias	Retrospective cohort	Mean initial dose 0.3 mg/kg/hr Mean infusion rate 0.42 mg/kg/hr (± 0.06) Max dose 0.6 mg/kg/hr Median duration of 43 hours (17-91)	Compared ketamine vs. nonketamine sedation
Radparvar et al, 2017, United States	32	Change in opioids or sedatives 72 hours pre- and post-initiation of ketamine	On target sedation, ICU complications, escalation of therapy	Poor quality, high risk of bias	Retrospective cohort	Not reported	Abstract only, ARDS patients, secondary outcomes not defined
Robinette et al, 2017, United States	56	Mechanical ventilation duration, on target sedation	Daily requirements of analgesics and sedatives, ICU delirium, ICU LOS, mortality	Poor quality, low risk of bias	Retrospective cohort	Not reported	Abstract only, no descriptive data stated (only comparisons between both groups)
Bucheit et al, 2017, United States	40	Slope of change in morphine equivalents (MEs) 12 hours pre- and post- ketamine infusion	Vasopressor requirements, RASS goal, vital signs	Poor quality, low risk of bias	Retrospective cohort	Mean starting dose and maintenance dose 0.3mg/kg/hr (± 0.57) Median duration 45.6 hr (23-74.4)	Surgical ICU population
Pruskowski et al, 2017, United States	36	Sedative and analgesic requirements	On target sedation, dosing patterns of adjunctive agents	Poor quality, low risk of bias	Retrospective cohort	Mean dose 0.77 mg/kg/hr (±0.51) 31 (86.1%) patients	Trauma patients

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						received ketamine for up to two days, and 22 (61.1%) remained on ketamine for 72 hours.	
Groetzinger et al, 2018, United States	91	% of Sedation-Agitation Scale (SAS) scores at goal*	Adverse events, reduction in concomitant sedatives*	Poor quality, high risk of bias	Retrospective cohort	Mean 0.41 mg/kg/hr (± 0.05) Median duration of 2.8 days (range up to 14.7 days)	Continuous ketamine infusion well tolerated in multi-subspecialty ICU setting
Reese et al, 2018, United States	46	Change in vasopressor requirement	Cumulative ketamine dose, additional sedative and analgesics (use and dose), corticosteroid use, mechanical ventilation days, lengths of stay, mortality	Good quality, low risk of bias	Prospective cohort, before-after	1-2 mg/kg bolus, then infusion starting at 5mcg/kg/min and titrated 2mcg/kg/min every 30 min.	17 patients received ketamine; multidisciplinary adult ICU

ICP: intracranial pressure; CPP: cerebral perfusion pressure; ICU: intensive care unit; LOS: length of stay; TBI: traumatic brain injury; SAH: subarachnoid hemorrhage; RASS: Richmond Agitation-Sedation Scale; ARDS: acute respiratory distress syndrome

*Primary and secondary outcomes were not specifically defined in the reporting of the study.

a Randomized trials assessed for bias using Cochrane collaboration tool. Full assessment is available in Supplemental Digital Content 3.
b Nonrandomized studies assessed for quality using Newcastle-Ottawa Scale. Full assessment is available in Supplemental Digital Content 3.

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FIGURE LEGENDS

Figure 1
Search, inclusion, and exclusion flow diagram

Figure 2
Forest plots displaying the impact of ketamine on fentanyl (A), midazolam (B), and propofol (C) dose

Figure 3
Forest plots displaying the impact of ketamine on intensive care unit length of stay (A), hospital length of stay (B), and mechanical ventilation duration (C)

Figure 4
Forest plots displaying the impact of ketamine on mortality (A), on-target sedation (B), vasopressor dependence (C), and delirium (D).

SUPPLEMENTAL MATERIALS LEGEND

Supplementary Text 1. Systematic review protocol and fully reproducible electronic search

Supplementary Table S1 and Supplementary Table S2. PRISMA and MOOSE Checklists

Supplementary Table S3. Cochrane Bias Assessment of Randomized Studies and Newcastle Ottawa Scale Quality Assessment for Nonrandomized Studies

Supplementary Table S4. Adverse effects of continuous ketamine infusion

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Supplementary Figure 1. Funnel plots for the outcomes of changes in fentanyl (A), midazolam (B), and propofol (C) doses

Author Statement

A Travis Manasco: Conceptualization, Methodology, Validation, Investigation, Resources, Data Curation, Writing- Original Draft, Writing- Review & Editing
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HIGHLIGHTS

- Despite a lack of high quality data, ketamine use is increasing for mechanically ventilated patients.
- There is an urgent need for more data regarding the benefit and potential adverse events associated with prolonged ketamine use in the intensive care unit.
- These results suggest that ketamine may play a role as a sedative-sparing agent, but may be associated with harm.
- High-quality studies are needed before widespread use or adoption of ketamine earlier in the sedation pathway.

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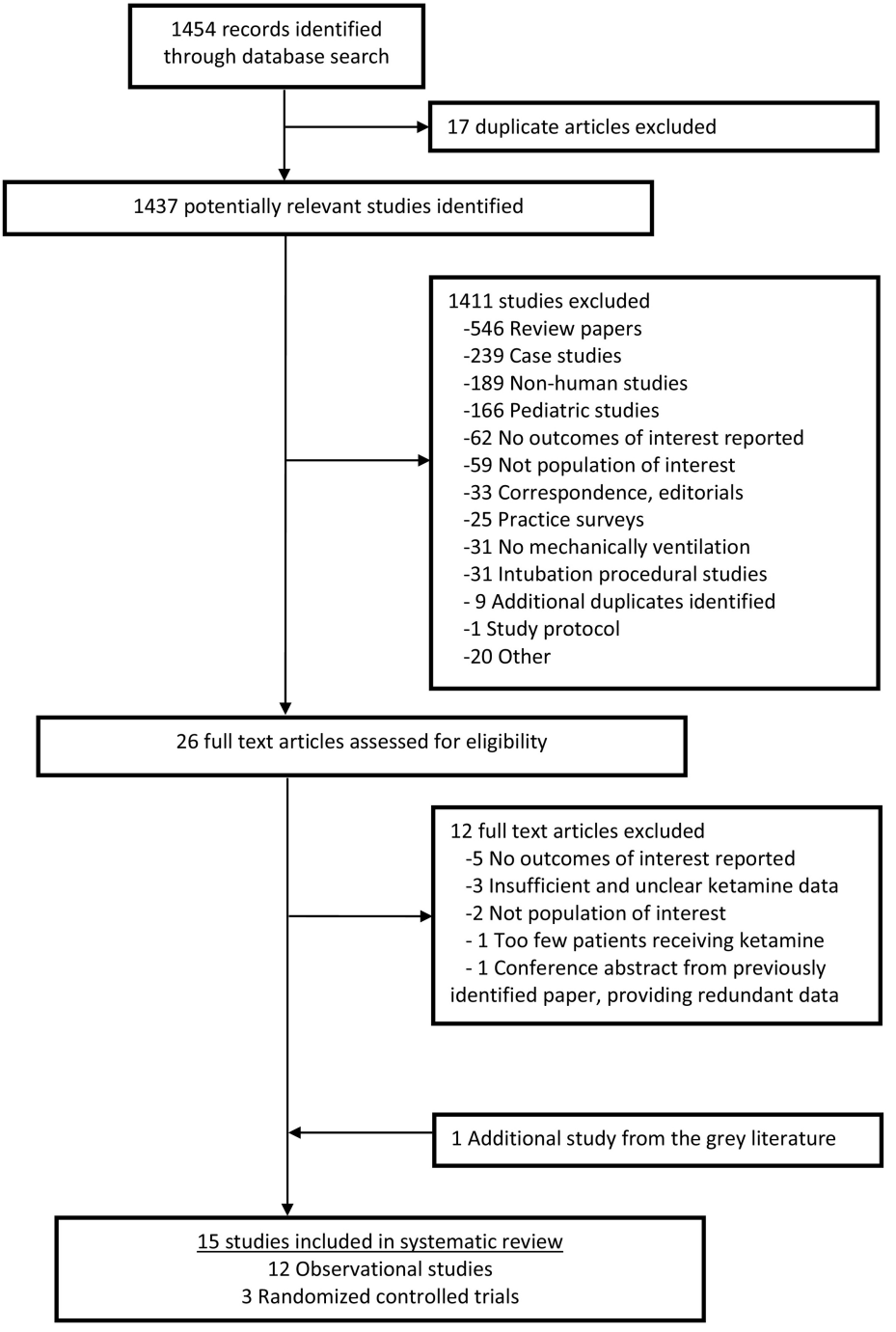
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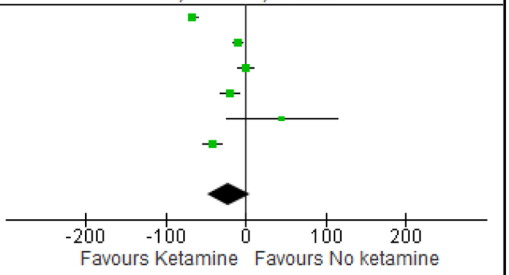
-239 Case studies
-189 Non-human studies
-166 Pediatric studies
-62 No outcomes of interest reported
-59 Not population of interest
-33 Correspondence, editorials
-25 Practice surveys
-31 No mechanically ventilation
-31 Intubation procedural studies
- 9 Additional duplicates identified
-1 Study protocol
-20 Other
26 full text articles assessed for eligibility
12 full text articles excluded
-5 No outcomes of interest reported
-3 Insufficient and unclear ketamine data
-2 Not population of interest
- 1 Too few patients receiving ketamine
- 1 Conference abstract from previously identified paper, providing redundant data
1 Additional study from the grey literature
15 studies included in systematic review
12 Observational studies
3 Randomized controlled trials

Figure 1

A

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	No ketamine Mean	No ketamine SD	No ketamine Total	Weight	Mean Difference IV, Random, 95% CI
Buchheit 2017	0	8.8	40	66	16.8	40	18.6%	-66.00 [-71.88, -60.12]
Garber 2019	125	25	98	135	16.6	98	18.6%	-10.00 [-15.94, -4.06]
Groetzinger 2018	200	32.5	82	200	29.4	82	18.3%	0.00 [-9.49, 9.49]
Pruskowski 2017	40	25	39	60	25	39	18.2%	-20.00 [-31.10, -8.90]
Radparvar 2017	213.7	146	32	168.5	136.7	32	8.3%	45.20 [-24.10, 114.50]
Reese 2018	7.3	9.7	17	48.9	30.5	29	18.1%	-41.60 [-53.62, -29.58]
Total (95% CI)			**308**			**320**	**100.0%**	**-21.54 [-48.18, 5.10]**

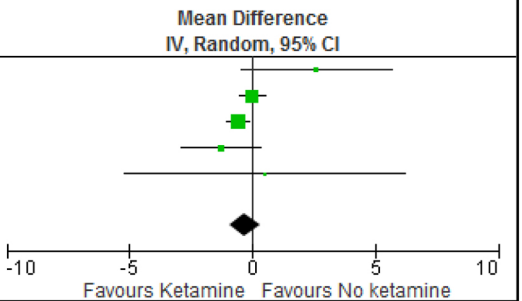
Heterogeneity: Tau² = 985.18; Chi² = 236.58, df = 5 (P < 0.00001); I² = 98%
Test for overall effect: Z = 1.58 (P = 0.11)



B

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	No ketamine Mean	No ketamine SD	No ketamine Total	Weight	Mean Difference IV, Random, 95% CI
Garber 2019	8.6	4.2	10	6	2.6	10	4.2%	2.60 [-0.46, 5.66]
Groetzinger 2018	1	1	33	1	1.2	33	39.7%	0.00 [-0.53, 0.53]
Perbet 2018	4.6	1.5	80	5.2	1.5	82	42.5%	-0.60 [-1.06, -0.14]
Pruskowski 2017	0.8	0.9	12	2.1	2.5	10	12.3%	-1.30 [-2.93, 0.33]
Radparvar 2017	12.2	11.2	32	11.7	12.1	32	1.3%	0.50 [-5.21, 6.21]
Total (95% CI)			**167**			**167**	**100.0%**	**-0.30 [-0.95, 0.35]**

Heterogeneity: Tau² = 0.20; Chi² = 7.74, df = 4 (P = 0.10); I² = 48%
Test for overall effect: Z = 0.90 (P = 0.37)



C

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	No ketamine Mean	No ketamine SD	No ketamine Total	Weight	Mean Difference IV, Random, 95% CI
Buchheit 2017	896	750	40	2,415	579	40	16.6%	-1519.00 [-1812.63, -1225.37]
Garber 2019	1,690	634	46	2,535	634	46	16.8%	-845.00 [-1104.10, -585.90]
Groetzinger 2018	2,117	382	37	2,166	491	45	17.2%	-49.00 [-238.02, 140.02]
Perbet 2018	1,747	630	80	1,889	610	82	17.2%	-142.00 [-333.02, 49.02]
Pruskowski 2017	1,997	408	18	3,057	568	27	16.6%	-1060.00 [-1345.36, -774.64]
Radparvar 2017	135	271	32	755	1,175	32	15.5%	-620.00 [-1037.80, -202.20]
Total (95% CI)			**253**			**272**	**100.0%**	**-699.34 [-1168.73, -229.95]**

Heterogeneity: Tau² = 323642.24; Chi² = 103.38, df = 5 (P < 0.00001); I² = 95%
Test for overall effect: Z = 2.92 (P = 0.003)

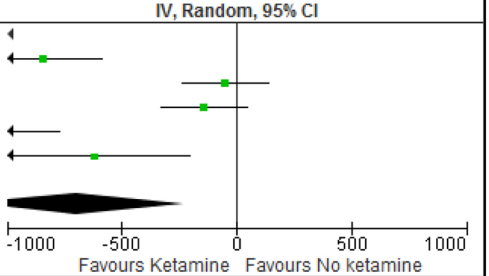
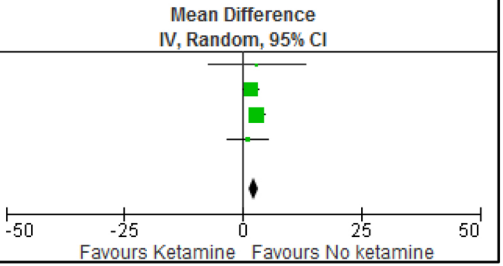


Figure 2

A

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	No ketamine Mean	No ketamine SD	No ketamine Total	Weight	Mean Difference IV, Random, 95% CI	Year
Bourgoin 2003	21	13	12	18	13	13	1.1%	3.00 [-7.20, 13.20]	2003
Perbet 2018	15.8	5.6	80	14	5.2	82	41.2%	1.80 [0.13, 3.47]	2018
Shurtleff 2018	11	4.3	39	8	2	40	51.7%	3.00 [1.51, 4.49]	2018
Reese 2018	11	7.1	17	10	7.6	29	6.0%	1.00 [-3.36, 5.36]	2018
Total (95% CI)			**148**			**164**	**100.0%**	**2.39 [1.32, 3.45]**	

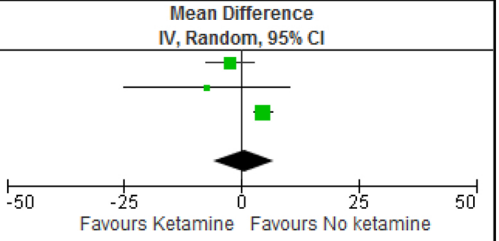
Heterogeneity: Tau² = 0.00; Chi² = 1.53, df = 3 (P = 0.67); I² = 0%
Test for overall effect: Z = 4.38 (P < 0.0001)



B

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	No ketamine Mean	No ketamine SD	No ketamine Total	Weight	Mean Difference IV, Random, 95% CI	Year
Reese 2018	15.9	7	17	18.4	11	29	39.2%	-2.50 [-7.71, 2.71]	2018
Winings 2018	32.4	18.9	8	39.8	38.6	40	10.6%	-7.40 [-25.14, 10.34]	2018
Shurtleff 2018	17.3	5.1	39	12.8	3.8	40	50.2%	4.50 [2.51, 6.49]	2018
Total (95% CI)			**64**			**109**	**100.0%**	**0.50 [-5.95, 6.95]**	

Heterogeneity: Tau² = 20.55; Chi² = 7.53, df = 2 (P = 0.02); I² = 73%
Test for overall effect: Z = 0.15 (P = 0.88)



C

Study or Subgroup	Ketamine Mean	Ketamine SD	Ketamine Total	No ketamine Mean	No ketamine SD	No ketamine Total	Weight	Mean Difference IV, Random, 95% CI	Year
Shurtleff 2018	8	5.9	39	7	2	40	25.6%	1.00 [-0.95, 2.95]	2018
Reese 2018	8.4	6.9	17	6.8	5.5	29	6.6%	1.60 [-2.24, 5.44]	2018
Perbet 2018	8.8	3.8	80	8.8	4	82	67.7%	0.00 [-1.20, 1.20]	2018
Total (95% CI)			**136**			**151**	**100.0%**	**0.36 [-0.63, 1.35]**	

Heterogeneity: Tau² = 0.00; Chi² = 1.16, df = 2 (P = 0.56); I² = 0%
Test for overall effect: Z = 0.72 (P = 0.47)

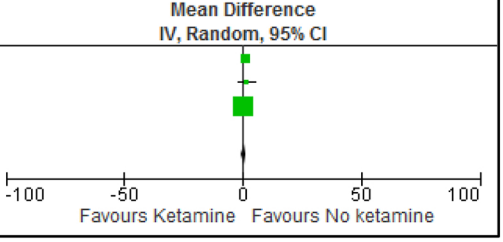
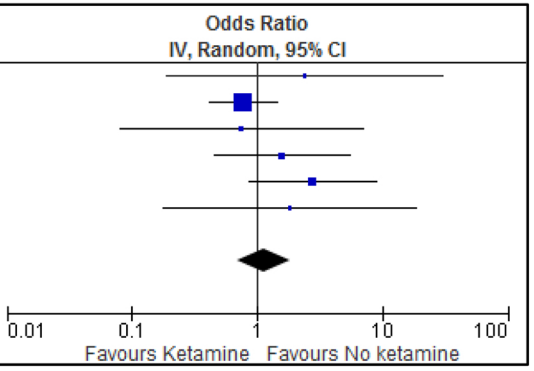


Figure 3

A

Study or Subgroup	Ketamine Events	Ketamine Total	No ketamine Events	No ketamine Total	Weight	Odds Ratio IV, Random, 95% CI
Bourgoin 2003	2	12	1	13	3.5%	2.40 [0.19, 30.52]
Perbet 2018	31	80	37	82	57.1%	0.77 [0.41, 1.44]
Quisilema-Cadena 2017	6	8	8	10	4.5%	0.75 [0.08, 6.96]
Reese 2018	7	17	9	29	14.4%	1.56 [0.45, 5.41]
Shurtleff 2018	11	39	5	40	16.4%	2.75 [0.86, 8.84]
Von der brelie 2016	3	41	1	24	4.1%	1.82 [0.18, 18.51]
Total (95% CI)		**197**		**198**	**100.0%**	**1.13 [0.70, 1.81]**
Total events	60		61			

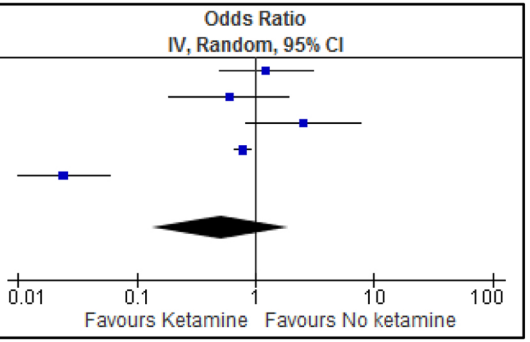
Heterogeneity: Tau² = 0.00; Chi² = 4.56, df = 5 (P = 0.47); I² = 0%
Test for overall effect: Z = 0.50 (P = 0.61)



B

Study or Subgroup	Ketamine Events	Ketamine Total	No ketamine Events	No ketamine Total	Weight	Odds Ratio IV, Random, 95% CI	Year
Buchheit 2017	17	40	15	40	20.0%	1.23 [0.50, 3.02]	2017
Pruskowski 2017	6	35	9	35	18.8%	0.60 [0.19, 1.91]	2017
Shurtleff 2018	12	39	6	40	19.1%	2.52 [0.84, 7.59]	2018
Groetzinger 2018	514	1325	565	1262	22.0%	0.78 [0.67, 0.91]	2018
Garber 2019	26	104	97	104	20.1%	0.02 [0.01, 0.06]	2019
Total (95% CI)		**1543**		**1481**	**100.0%**	**0.51 [0.14, 1.88]**	
Total events	575		692				

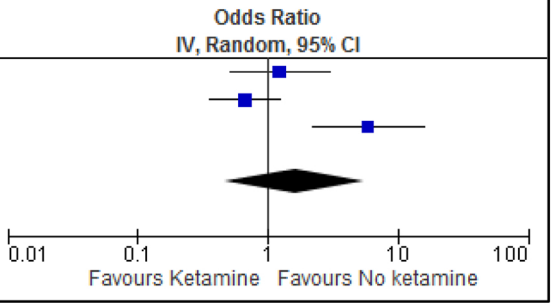
Heterogeneity: Tau² = 2.03; Chi² = 63.97, df = 4 (P < 0.00001); I² = 94%
Test for overall effect: Z = 1.02 (P = 0.31)



C

Study or Subgroup	Ketamine Events	Ketamine Total	No ketamine Events	No ketamine Total	Weight	Odds Ratio IV, Random, 95% CI
Buchheit 2017	18	40	16	40	32.8%	1.23 [0.51, 2.98]
Groetzinger 2018	25	91	33	91	35.8%	0.67 [0.36, 1.25]
Shurtleff 2018	31	39	17	43	31.5%	5.93 [2.20, 15.93]
Total (95% CI)		**170**		**174**	**100.0%**	**1.62 [0.47, 5.56]**
Total events	74		66			

Heterogeneity: Tau² = 1.01; Chi² = 13.38, df = 2 (P = 0.001); I² = 85%
Test for overall effect: Z = 0.76 (P = 0.44)



D

Study or Subgroup	Ketamine Events	Ketamine Total	No ketamine Events	No ketamine Total	Weight	Odds Ratio IV, Random, 95% CI
Perbet 2018	17	80	30	82	72.2%	0.47 [0.23, 0.94]
Shurtleff 2018	29	39	34	40	27.8%	0.51 [0.17, 1.58]
Total (95% CI)		**119**		**122**	**100.0%**	**0.48 [0.26, 0.87]**
Total events	46		64			

Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%
Test for overall effect: Z = 2.42 (P = 0.02)

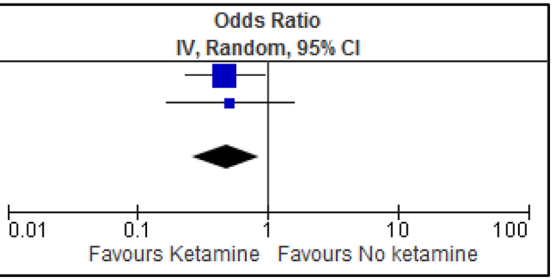


Figure 4